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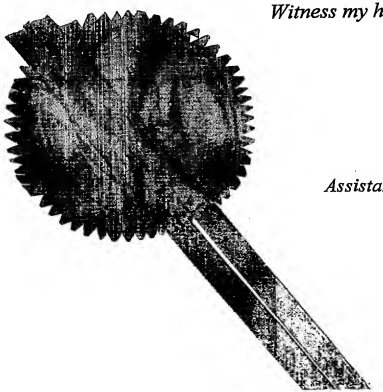
INTELLECTUAL PROPERTY INDIA

*GOVERNMENT OF INDIA*
*MINISTRY OF COMMERCE & INDUSTRY*
*PATENT OFFICE, DELHI BRANCH*
*W - 5, WEST PATEL NAGAR*
*NEW DELHI - 110 008.*

*I, the undersigned being an officer duly authorized in accordance with the provision of the Patent Act, 1970 hereby certify that annexed hereto is the true copy of the* ***Application*** *and* ***Complete Specification*** *filed in connection with Application for Patent No.* ***1445/Del/2003*** *dated* ***21st November 2003.***

*Witness my hand this 13th day of January 2005.*



*(S.K. PANGASA)*
*Assistant Controller of Patents & Designs*

1445 DEL/03

21 NOV 2003

# THE PATENTS ACT, 1970
(39 of 1970)

## APPLICATION FOR GRANT OF A PATENT
(See Sections 5(2), 7, 54 and 135; and rule 39)

1. We, **RANBAXY LABORATORIES LIMITED**, a Company incorporated under the Companies Act, 1956, Corporate Office at 19, Nehru Place, New Delhi - 110 019, India

2. hereby declare –

(a) that we are in possession of an invention titled **"A PROCESS FOR THE PREPARATION OF PHARMACEUTICAL COMPOSITIONS OF NATEGLINIDE"**

(b) that the Complete Specification relating to this invention is filed with this application.

(c) that there is no lawful ground of objection to the grant of a patent to us.

3. Further declare that the inventors for the said invention are

a. ROMI BARAT SINGH
b. ANU SHILPA
c. VISHNUBHOTLA NAGA PRASAD
d. SANJEEV KUMAR SETHI

of Ranbaxy Laboratories Limited, Plot No. 20, Sector-18, Udyog Vihar Industrial Area, Gurgaon – 122001 (Haryana), India, all Indian Nationals.

4. We claim the priority from the application(s) filed in convention countries, particulars of which are as follows: **NOT APPLICABLE**

5. We state that the said invention is an improvement in or modification of the invention, the particulars of which are as follows and of which we are the applicant: **PATENT APPLICATION NO. 1003/DEL/2003 FILED ON 14.08.2003.**

6. We state that the application is divided out of our application, the particulars of which are given below and pray that this application deemed to have been filed on ..... Under section 16 of the Act. **NOT APPLICABLE**

7. That we are the assignee or legal representatives of the true and first inventors.

8. That our address for service in India is as follows:

**DR. B. VIJAYARAGHAVAN**
**Associate Director – Intellectual Property**
Ranbaxy Laboratories Limited
Plot No.20, Sector – 18, Udyog Vihar Industrial Area,
Gurgaon – 122001 (Haryana). INDIA.
Tel. No. (91-124) 2343126, 2342001–10; 5012501-10

9. Following declaration was given by the inventors or applicants in the convention country:

We, ROMI BARAT SINGH, ANU SHILPA, VISHNUBHOTLA NAGA PRASAD, SANJEEV KUMAR SETHI of Ranbaxy Laboratories Limited, Plot No. 20, Sector – 18, Udyog Vihar Industrial Area, Gurgaon–122001 (Haryana), India, all Indian Nationals, the true and first inventors for this invention or applicant in the convention country declare that the applicant herein, **Ranbaxy Laboratories Limited**, Corporate Office at 19, Nehru Place, New Delhi - 110 019, India, is our assignee or legal representatives.

a. Romi Singh

(ROMI BARAT SINGH)

b. Shilpa

(ANU SHILPA)

c. V. Nagaprasad

(VISHNUBHOTLA NAGA PRASAD)

d.

( SANJEEV KUMAR SETHI)

10. That to the best of our knowledge, information and belief the fact and matters stated herein are correct and that there is no lawful ground of objection to the grant of patent to us on this application.

11. Followings are the attachment with the application:
    a. Provisional Specification (3 copies)
    b. Drawings (3 copies)
    c. Priority document(s)
    d. Statement and Undertaking on FORM – 3
    e. Power of Authority (Not required)
    f. Fee Rs.3,000/- (Rupees Three Thousand only..) in cheque bearing No. dated : drawn on

We request that a patent may be granted to us for the said invention.

Dated this 21ST day of **November, 2003.**

**For Ranbaxy Laboratories Limited**

Sen

(SUSHIL KUMAR PATAWARI)
**Company Secretary**

1445-DEL-03

FORM 2

21 NOV 2003

The Patents Act, 1970

(39 of 1970)

# COMPLETE SPECIFICATION

( See Section 10 )

# A PROCESS FOR THE PREPARATION OF PHARMACEUTICAL COMPOSITIONS OF NATEGLINIDE

RANBAXY LABORATORIES LIMITED
19, NEHRU PLACE, NEW DELHI - 110019

*A Company incorporated under the Companies Act, 1956.*

The following specification particularly describes and ascertains the nature of this invention and the manner in which it is to be performed:

The present invention relates to pharmaceutical compositions of Nateglinide with 50-70% of water-soluble filler alone or in combination with a channeling agent.

Nateglinide is an amino acid derivative that lowers blood glucose levels by stimulating insulin secretion from the pancreas. It is widely indicated as monotherapy to lower blood glucose in patients with Type 2 diabetes. It is also indicated for use in combination with Metformin.

Presently Nateglinide oral tablets are available in 60mg or 120mg strengths and are marketed by Novartis under the trade name STARLIX.

As the active agent, in particular drug substance for the composition, Nateglinide is described in EP 196222 and EP 526171.The active drug substance can be present as its pharmaceutically acceptable salts selected from acid addition salts, for example, as a sodium or as a maleate or hydrochloride.

Nateglinide has a poor solubility, hence the desired dissolution is difficult to achieve.

Prior art patent US 6,559,188 describe compositions of Nateglinide or a pharmaceutically acceptable salt thereof. All the examples given in US 6559188 make use of lactose and microcrystalline cellulose as filler, one of which is water-soluble and other water insoluble. The concentration of lactose (water-soluble filler) being 34 to 36% w/w and microcrystalline cellulose (water insoluble filler) 17 to 23% w/w, the total concentration of filler ranging from 50-70% w/w.

We discovered that Nateglinide tablets when prepared with 50-70% w/w of a water-soluble filler alone shows a dissolution profile wherein atleast 70% of the drug is released within 45 minutes.

Further we have also discovered that use of atleast one channeling agent in the core along with water-soluble filler, further improves the dissolution.

Present invention provides more flexibility and choice of pharmaceutical excipients like binders and fillers.

The water-soluble fillers can be selected from the group comprising of lactose, white sugar, sucrose, glucose, sorbitol and the like.

Channeling agents may be selected from excipients like a sugar, a sugar alcohol, a salt, or mixtures of any of these compounds. The channeling agents have better solubility than water-soluble filler.

The invention is directed to a surprising and unexpected discovery of use of water-soluble fillers in concentration of 50-70% w/w alone or in combination with channeling agents to enhance the solubility and dissolution of solid dose oral formulations of poorly soluble drugs like Nateglinide.

Hence in one aspect it provides an oral solid composition comprising Nateglinide in a free or pharmaceutically acceptable salt form and a water-soluble filler wherein its concentration is in the range of 50-70% w/w.

In another aspect it provides an oral solid composition.comprising Nateglinide in a free or pharmaceutically acceptable salt form, a water-soluble filler and a channeling agent. The channeling agent due to its better water solubility gets solubilized in water, or gastrointestinal fluid thus forming channels through which the water or the Gastrointestinal fluid is ingressed into the formulation and hence aids in dissolution.

In another aspect it provides an oral solid composition comprising Nateglinide in a free or pharmaceutically acceptable salt form, a water-soluble filler and a channeling agent wherein the water-soluble filler is selected from a group comprising of lactose, white sugar, sucrose, glucose, sorbitol and the like.

In another aspect it provides an oral solid composition comprising Nateglinide in a free or pharmaceutically acceptable salt form, a water-soluble filler, and a channeling agent wherein the channeling agent is selected from water soluble excipients like a sugar, a sugar alcohol, a salt, or mixtures thereof.

In another aspect it provides an oral solid composition comprising Nateglinide in a free or pharmaceutically acceptable salt form, a water-soluble filler and a channeling agent wherein the channeling agent is a sugar selected from compressible sugar, glucose. mannose and the like.

In another aspect it provides an oral solid composition comprising Nateglinide in a free or pharmaceutically acceptable salt form, a water-soluble filler and a channeling agent wherein the channeling agent is a salt selected from sodium chloride, potassium chloride and the like.

In another aspect it provides an oral solid composition comprising Nateglinide in a free or pharmaceutically acceptable salt form, a water-soluble filler and a channeling agent wherein the channeling agent is a sugar alcohol selected from mannitol, sorbitol, xylitol, erythritol, lactitol, or maltitol and the like.

In another aspect it provides an oral solid composition comprising Nateglinide in a free or pharmaceutically acceptable salt form, a water-soluble filler in a concentration range of 50-70% w/w and at least one other antidiabetic compound.

In another aspect it provides an oral solid composition comprising Nateglinide in a free or pharmaceutically acceptable salt form; a water-soluble filler, a channeling agent and at least one other antidiabetic compound.

In another aspect it provides an oral solid composition comprising Nateglinide in a free or pharmaceutically acceptable salt form; a water-soluble filler, a channeling agent and at least one other antidiabetic compound selected from the group consisting of glitazones,

sulfonyl urea derivatives and metformin in each case in free form or in form of a pharmaceutically acceptable salt thereof.

In another aspect it provides a method of preparing an oral solid composition comprising Nateglinide in a free or pharmaceutically acceptable salt and 50-70% w/w of water-soluble filler alone or in combination with a channeling agent.

In another aspect it provides an oral solid composition comprising Nateglinide in a free or pharmaceutically acceptable salt form and a water-soluble filler in the concentration range of 50-70%w/w, for the preparation of a medicament for the prevention, delay of progression or treatment of metabolic disorders, in particular of type 2 diabetes mellitus or a disease or condition associated with diabetes mellitus.

In another aspect it provides an oral solid composition comprising Nateglinide in a free or pharmaceutically acceptable salt form, a water-soluble filler and a channeling agent for the preparation of a medicament for the prevention, delay of progression or treatment of metabolic disorders, in particular of type 2 diabetes mellitus or a disease or condition associated with diabetes mellitus.

In another aspect it provides an oral solid composition comprising Nateglinide in a free or pharmaceutically acceptable salt and a water-soluble filler in the concentration range of 50-70%w/w wherein atleast 70% by weight of nateglinide is released within a forty five minute period.

In another aspect it provides an oral solid composition comprising Nateglinide in a free or pharmaceutically acceptable salt form, a water-soluble filler and a channeling agent wherein atleast 70% by weight of nateglinide is released within a forty five minute period.

The oral solid composition as described herein may include other pharmaceutically acceptable excipients in addition to Nateglinide and channeling agent.

The term 'Nateglinide' as used herein includes Nateglinide in a free or pharmaceutically acceptable salt form selected from an acid addition salt, for example as a sodium salt or as a maleate. In particular, the composition comprises the B- or H-type crystal modification of Nateglinide, more particularly the H-type. The active ingredient or a pharmaceutically acceptable salt thereof may also be used in form of a hydrate or include other solvents used for crystallization.

The dosage range of the nateglinide depends upon factors known to the person skilled in the art including species of the warm-blooded animal, body weight and age, the nature and severity of the condition to be treated, and the mode of administration to be employed. Unless stated otherwise herein, Nateglinide is preferably divided and administered from one to four times per day.

Nateglinide is preferably administered to the warm-blooded animal in a dosage in the range of about 5 to 1200, more preferably 10 to 1000 and most preferably 25 to 800 mg/day, especially when the warm-blooded animal is a human of about 70 kg body weight.

'Channeling agents' as used herein includes water-soluble excipients, which gets solubilized in water, or Gastrointestinal fluid thus forming channels through which the water or the Gastrointestinal fluid is ingressed into the formulation and hence aids in dissolution. The channeling agent may be selected from a group consisting of; sugar selected from compressible sugar, glucose, or mannose; a salt selected from sodium chloride, or potassium chloride; a sugar alcohol, selected from mannitol, sorbitol, xylitol, erythritol, lactitol, or maltitol; or a mixture thereof.

The term 'other pharmaceutically acceptable excipient' refers to ingredients of the composition, excluding the active drug substance.

Examples of other pharmaceutically acceptable excipients as used herein include fillers, binders, disintegrants, lubricants, glidants, colors and the like.

The fillers can be selected from the group comprising of corn starch, lactose, white sugar, sucrose, glucose, sorbitol, calcium carbonate, calcium phosphate-dibasic, calcium phosphate-tribasic, calcium sulfate, microcrystalline cellulose, silicified microcrystalline cellulose, cellulose powdered, dextrates, dextrins, dextrose, fructose, kaolin, lactitol, mannitol, sorbitol, starch, starch pregelatinized, and the like.

Examples of binders include methyl cellulose, hydroxypropyl cellulose, hydroxy propyl methyl cellulose , polyvinylpyrrolidone, gelatin, gum Arabic, ethyl cellulose, polyvinyl alcohol, pullulan, pregelatinized starch, agar, tragacanth, sodium alginate, propylene glycol, and the like.

Examples of disintegrants include starch, croscarmellose sodium, crospovidone, polacrillin potassium, sodium starch glycolate and the like.

Examples of lubricants and glidants include colloidal anhydrous silica, stearic acid, magnesium stearate, calcium stearate, talc, hydrogenated castor oil, sucrose esters of fatty acids, microcrystalline wax, yellow beeswax, white beeswax and the like.

The coloring agents of the present invention may be selected from any FDA approved colors for oral use.

Nateglinide or pharmaceutically acceptable salt thereof may be present in any amount which is sufficient to elicit a therapeutic effect and, where applicable, may be present either substantially in the form of one optically pure enantiomer or as a mixture, racemic or otherwise, of enantiomers.

Nateglinide can be present in an amount of about 5% to about 70% (w/w), and most preferably about 15% to about 40% (w/w), based on the total weight of the dry composition.

The channeling agents can be present in an amount of about 5% to about 30% (w/w), and most preferably about 10% to about 25% (w/w), by weight based on the total weight of the dry composition.

The solid dose formulation can be prepared by processes known in the prior art selected from wet granulation, dry granulation or direct compression and may be in the form of tablet or capsule.

In one of the embodiments nateglinide tablet may be prepared by blending nateglinide, water-soluble filler with or without a channeling agent and disintegrant; granulating the blend with a binder solution; drying the granules; sizing; lubricating and compressing the lubricated granules.

In another embodiment nateglinide tablet may be prepared by blending nateglinide, water-soluble filler, with or without a channeling agent, disintegrant and binder; granulating the blend with a solvent; drying the granules; sizing; lubricating and compressing the lubricated granules.

Granulation may be carried out in fluidized bed dryer and sizing can be done by milling or pulverization.

In another embodiment nateglinide tablet may be prepared by blending nateglinide, water-soluble filler with or without a channeling agent, disintegrant and binder; compacting or slugging the blend; breaking the slugs to make granules; lubricating and compressing the lubricated granules.

In another embodiment nateglinide tablet may be prepared by blending nateglinide, water-soluble filler with or without a channeling agent, disintegrant, binder and lubricant; and compressing.

The tablets prepared by the present invention may be coated with one or more additional layers comprising film forming agents and/or pharmaceutically acceptable excipients.

The coating layers over the tablet may be applied as solution/ dispersion of coating ingredients using any conventional technique known in the prior art selected from spray coating in a conventional coating pan or fluidized bed processor; dip coating and the like.

Example of solvents used for preparing a solution/dispersion of the coating ingredients include methylene chloride, isopropyl alcohol, acetone, methanol, ethanol, water and the like and mixtures thereof.

Example of film forming agents include ethyl cellulose, Hydroxypropyl methylcellulose, Hydroxypropyl cellulose, methyl cellulose, carboxymethylcellulose, hydroxymethylcellulose, hydroxyethylcellulose, hydroxypropyl methyl phthalate, cellulose acetate, cellulose acetate trimelliatate, cellulose acetate phthalate; Waxes selected from polyethylene glycol; methacrylic acid polymers selected from Eudragit ® RL and RS; and the like and mixture thereof. Alternatively, commercially available coating compositions comprising film-forming polymers marketed under various trade names, selected from Opadry® may also be used for coating.

The following examples are illustrative of the invention, and are not to be construed as limiting the invention.

**Example 1**

| Ingredient | Quantity (wt/tablet) mg |
|---|---|
| Nateglinide | 121.21* |
| Lactose | 424.16 |
| Povidone | 12 |
| Croscarmellose sodium | 20 |
| Colloidal silicon dioxide | 16 |
| Purified water | q.s |
| Croscarmellose Sodium | 12.8 |
| Colloidal silicon dioxide | 12.8 |
| Magnesium stearate | 11.4 |

** Equivalent to Nateglinide 120mg after potency and moisture adjustment*

PROCEDURE:

1. Nateglinide along with lactose, povidone, colloidal silicon dioxide and a part of croscarmellose sodium are mixed in a high shear mixer and granulated using purified water.
2. The wet granules are dried in a fluid bed drier, passed through a screen and then subjected to sizing.
3. The colloidal silicon dioxide and the rest of the croscarmellose sodium are mixed, passed through a screen and blended with the granules of step 2.
4. The magnesium stearate is passed through a screen, blended with the blend of step 3 and the total mixture is compressed to tablets.

**Example 2**

| Ingredient | Quantity (wt/tablet) mg |
|---|---|
| Nateglinide | 121.21* |
| Lactose | 343.79 |
| Sodium chloride | 80 |
| Povidone | 12 |
| Croscarmellose sodium | 20 |
| Colloidal silicon dioxide | 16 |
| Purified water | q.s |
| Croscarmellose Sodium | 12.8 |
| Colloidal silicon dioxide | 12.8 |
| Magnesium stearate | 11.4 |

** Equivalent to Nateglinide 120mg after potency and moisture adjustment*

PROCEDURE:

1. Nateglinide along with lactose, sodium chloride, povidone, colloidal silicon dioxide and a part of croscarmellose sodium are mixed in a high shear mixer and granulated using purified water.
2. The wet granules are dried in a fluid bed drier, passed through a screen and then subjected to sizing.
3. The colloidal silicon dioxide and the rest of the croscarmellose sodium are mixed, passed through a screen and blended with the granules of step 2.
4. The magnesium stearate is passed through a screen, blended with the blend of step 3 and the total mixture is compressed to tablets.

**Example 3**

| Ingredient | Quantity (wt/tablet) mg |
|---|---|
| Nateglinide | 121.21* |
| Lactose | 343.79 |
| Compressible sugar | 100 |
| Povidone | 12 |
| Croscarmellose sodium | 20 |
| Colloidal silicon dioxide | 16 |
| Purified water | q.s |
| Croscarmellose Sodium | 12.8 |
| Colloidal silicon dioxide | 12.8 |
| Magnesium stearate | 11.4 |

** Equivalent to Nateglinide 120mg after potency and moisture adjustment*

PROCEDURE:

1. Nateglinide along with lactose, compressible sugar, povidone, colloidal silicon dioxide and a part of croscarmellose sodium are mixed in a high shear mixer and granulated using purified water.
2. The wet granules are dried in a fluid bed drier, passed through a screen and then subjected to sizing.
3. The colloidal silicon dioxide and the rest of the croscarmellose sodium are mixed, passed through a screen and blended with the granules of step 2.

4. The magnesium stearate is passed through a screen, blended with the blend of step 3 and the total mixture is compressed to tablets.

*In vitro* dissolution study

*In vitro* release of nateglinide from tablets as per composition of Example 1-3 was studied in 1000 ml, 0.01 N HCl, with 0.5% SLS (pH–1.2), using USP apparatus – II, at 50 rpm. The results are listed in Table 1.

Table 1: In vitro release of nateglinide from tablets

| Time | Cumulative percentage (%) release of nateglinide from Tablets | | | |
|---|---|---|---|---|
| | STARLIX | Example 1 | Example 2 | Example 3 |
| 10 | 62 | 40 | 62 | 66 |
| 20 | - | 43 | - | - |
| 30 | 65 | 72 | 76 | 80 |
| 45 | 67 | 77 | 83 | 87 |
| 60 | 72 | - | - | - |
| Infinity | 93 | 96 | 96 | 96 |

Table 1 clearly indicates that compositions containing water-soluble filler alone (Example 1), or in combination with channeling agent (Example 2 and 3) show a dissolution profile comparable to STARLIX.

While there has been shown and described what are the preferred embodiments of the invention, one skilled in the pharmaceutical formulation art will appreciate that various modifications in the formulations and process can be made without departing from the scope of the invention as it is defined by the appended claims.

## WE CLAIM:

1. An oral solid composition of Nateglinide comprising:

   a) Nateglinide or pharmaceutically acceptable salts thereof: and

   b) a water-soluble filler in a concentration range of 50-70%w/w

   wherein atleast 70% by weight of Nateglinide is released within 45 minute period.

2. The oral solid composition of Nateglinide according to claim 1 wherein the water-soluble filler is selected from a group of lactose, white sugar, sucrose, glucose, sorbitol and mixtures thereof.

3. The oral solid composition of Nateglinide according to claim 2 wherein the water-soluble filler is lactose.

4. The oral solid composition according to claim 1 wherein in addition to Nateglinide and water-soluble filler, it comprises of other pharmaceutically acceptable excipients selected from a group consisting of binder, disintegrant, lubricant, coloring and flavoring agent.

5. The oral solid composition according to claim 4 wherein binder is selected from methyl cellulose, hydroxypropyl cellulose, hydroxy propyl methyl cellulose , povidone, gelatin, gum Arabic, ethyl cellulose, polyvinyl alcohol, pullulan, pregelatinized starch, agar, tragacanth, sodium alginate, propylene glycol, and mixtures thereof.

6. The oral solid composition according to claim 5 wherein binder is povidone.

7. The oral solid composition according to claim 4 wherein disintegrant is selected from starch, croscarmellose sodium, crospovidone, sodium starch glycolate , polacrillin potassium and mixtures thereof.

8. The oral solid composition according to claim 7 wherein disintegrant is croscarmellose sodium.

9. The oral solid composition according to claim 4 wherein lubricant is selected from colloidal anhydrous silica, stearic acid, magnesium stearate, calcium stearate, talc,

hydrogenated castor oil, sucrose esters of fatty acids, microcrystalline wax, yellow beeswax, white beeswax and the like.

10. The oral solid composition according to claim 9 wherein lubricant is magnesium stearate.

11. The oral solid composition according to claim 1 wherein it is in the form of a tablet.

12. The oral solid composition according to claim 1 wherein it is in the form of a capsule.

13. The oral solid composition according to claim 11 wherein the tablet is further coated with one or more functional and/or non-functional layers.

14. A process for preparation of oral tablet of Nateglinide comprising:

a) Nateglinide or pharmaceutically acceptable salts thereof; and

b) a water-soluble filler in a concentration range of 50-70%w/w

by wet granulation, dry granulation or direct compression, wherein atleast 70% by weight of Nateglinide is released within 45 minute period.

15. The process for preparation of oral tablet of Nateglinide according to claim 14, wherein in addition to Nateglinide and water-soluble filler it also comprises of other pharmaceutically acceptable excipients.

16. The process for preparation of oral tablet of Nateglinide according to claim 15, wherein other pharmaceutically acceptable excipients are selected from a group consisting of binder, disintegrant, lubricant, coloring and flavoring agent.

17. The process for preparation of oral tablet of Nateglinide according to claim 16, by blending Nateglinide, water-soluble filler and disintegrant; granulating the blend with a binder solution; drying the granules; sizing; lubricating and compressing the lubricated granules.

18. The process for preparation of oral tablet of Nateglinide according to claim 16, by blending Nateglinide, water-soluble filler, disintegrant and binder; granulating the blend with a solvent; drying the granules; sizing; lubricating and compressing the lubricated granules.

19. The process for preparation of oral tablet of Nateglinide according to claim 16, by blending Nateglinide, water-soluble filler, disintegrant and binder; compacting or slugging the blend; breaking the slugs to make granules; lubricating and compressing the lubricated granules.

20. The process for preparation of oral tablet of Nateglinide according to claim 16, by blending nateglinide, water-soluble filler, disintegrant, binder and lubricant; and compressing.

21. A medicament for the prevention, delay of progression or treatment of metabolic disorders, in particular of type 2 diabetes mellitus or a disease or condition associated with diabetes mellitus comprising:

a) Nateglinide or pharmaceutically acceptable salts thereof; and

b) a water-soluble filler in a concentration range of 50-70%w/w

22. An oral solid composition of Nateglinide comprising:

a) Nateglinide or pharmaceutically acceptable salts thereof;

b) a water-soluble filler; and

c) at least one pharmaceutically acceptable channeling agent,

wherein atleast 70% by weight of Nateglinide is released within 45 minute period.

23. The oral solid composition of Nateglinide according to claim 22 wherein the water-soluble filler is selected from a group of lactose, white sugar, sucrose, glucose, sorbitol, and the like.

24. The oral solid composition of Nateglinide according to claim 23 wherein the water-soluble filler is lactose.

25. The oral solid composition of Nateglinide according to claim 22 wherein the channeling agent is selected from a sugar, a salt or a sugar alcohol, or combinations thereof.

26. The oral solid composition of Nateglinide according to claim 25 wherein the channeling agent is a sugar selected from compressible sugar, glucose, mannose and the like.

27. The oral solid composition of Nateglinide according to claim 25 wherein the channeling agent is a salt selected from sodium chloride, potassium chloride and the like.

28. The oral solid composition of Nateglinide according to claim 25 wherein the channeling agent is a sugar alcohol selected from mannitol, sorbitol, xylitol, erythritol, lactitol, or maltitol and the like.

29. The oral solid composition of Nateglinide according to claim 26 wherein the channeling agent is compressible sugar.

30. The oral solid composition of Nateglinide according to claim 27 wherein the channeling agent is sodium chloride.

31. The oral solid composition according to claim 22 wherein in addition to Nateglinide, water-soluble filler and channeling agent comprise other pharmaceutically acceptable excipients selected from a group consisting of binder, disintegrant, lubricant, coloring and flavoring agent as herein described are also present.

32. The oral solid composition according to claim 31 wherein binder is selected from methyl cellulose, hydroxypropyl cellulose, povidone, gelatin, gum Arabic, ethyl cellulose, polyvinyl alcohol, pullulan, pregelatinized starch, agar, tragacanth, sodium alginate, propylene glycol, and the like.

33. The oral solid composition according to claim 32 wherein binder is povidone.

34. The oral solid composition according to claim 31 wherein disintegrant is selected from starch, croscarmellose sodium, crospovidone, sodium starch glycolate and the like.

35. The oral solid composition according to claim 34 wherein disintegrant is croscarmellose sodium.

36. The oral solid composition according to claim 31 wherein lubricant is selected from colloidal anhydrous silica, stearic acid, magnesium stearate, calcium stearate, talc, hydrogenated castor oil, sucrose esters of fatty acids, microcrystalline wax, yellow beeswax, white beeswax and the like.

37. The oral solid composition according to claim 36 wherein lubricant is magnesium stearate.

38. The oral solid composition according to claim 22 wherein it is in the form of a tablet.

39. The oral solid composition according to claim 22 wherein it is in the form of a capsule.

40. The oral solid composition according to claim 38 wherein the tablet is further coated with one or more functional and/or non-functional layers.

41. A process for preparation of oral tablet of Nateglinide comprising:

a) Nateglinide or pharmaceutically acceptable salts thereof;

b) a water-soluble filler; and

c) at least one pharmaceutically acceptable channeling agent,

by wet granulation, dry granulation or direct compression, wherein atleast 70% by weight of Nateglinide is released within 45 minute period.

42. The process for preparation of oral tablet of Nateglinide according to claim 41, wherein in addition to Nateglinide, water-soluble filler and channeling agent it also comprises of other pharmaceutically acceptable excipients.

43. The process for preparation of oral tablet of Nateglinide according to claim 42, wherein other pharmaceutically acceptable excipients are selected from a group consisting of binder, disintegrant, lubricant, coloring and flavoring agent.

44. The process for preparation of oral tablet of Nateglinide according to claim 43, by blending Nateglinide, water-soluble filler, channeling agent, and disintegrant; granulating the blend with a binder solution; drying the granules; sizing; lubricating and compressing the lubricated granules.

45. The process for preparation of oral tablet of Nateglinide according to claim 43, by blending Nateglinide, water-soluble filler, channeling agent, disintegrant and binder; granulating the blend with a solvent; drying the granules; sizing; lubricating and compressing the lubricated granules.

46. The process for preparation of oral tablet of Nateglinide according to claim 43, by blending Nateglinide, water-soluble filler, channeling agent, disintegrant and

binder; compacting or slugging the blend; breaking the slugs to make granules; lubricating and compressing the lubricated granules.

47. The process for preparation of oral tablet of Nateglinide according to claim 43, by blending nateglinide, water-soluble filler, channeling agent, disintegrant, binder and lubricant; and compressing.

48. A medicament for the prevention, delay of progression or treatment of metabolic disorders, in particular of type 2 diabetes mellitus or a disease or condition associated with diabetes mellitus comprising:

a) Nateglinide or pharmaceutically acceptable salts thereof;

b) water-soluble filler; and

c) at least one pharmaceutically acceptable channeling agent.

49. A oral solid composition of Nateglinide comprising:

a) Nateglinide or pharmaceutically acceptable salts thereof;

b) water-soluble filler; and

c) at least one pharmaceutically acceptable channeling agent,

wherein atleast 70% by weight of Nateglinide is released within 45 minute period as described and illustrated herein.

Dated this 21ST day of **November. 2003.**

**For Ranbaxy Laboratories Limited**

**(SUSHIL KUMAR PATAWARI)**
**COMPANY SECRETARY**

## ABSTRACT

A PROCESS FOR THE PREPARATION OF PHARMACEUTICAL COMPOSITIONS OF NATEGLINIDE

The present invention relates to pharmaceutical compositions of Nateglinide with 50-70% of water-soluble filler alone or in combination with a channeling agent. These compositions show a dissolution profile wherein at least 70% by weight of Nateglinide is released within 45 minute period.